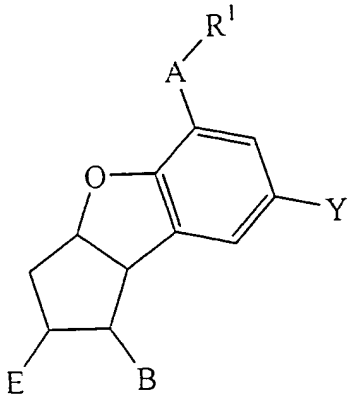
395, 281-284 (1998)). It is known that compounds which specifically bind to EP4 receptor subtype are effective for prevention, therapy or amelioration of immune diseases, asthma, osteodystrophy, apoptosis of neurocytes, hepatopathy, nephritis, hypertension, myocardial ischemia, gastrointestinal disorder, shock and the like (Japanese Laid-open Patent Application (Kokai) No. 10-265454, WO98/55468). However, it is not known that these compounds have hair generation- or hair growth-modulating actions.--

IN THE CLAIMS:

Please cancel claims 1-16 and 18 without prejudice to or disclaimer of the subject matter disclosed therein.

Please amend the claims as follows:

17. (Amended) A method for modulating growth or generation of hair comprising administering a prostaglandin EP4 receptor ligand in an amount effective for modulating growth or generation of hair to human or an animal; wherein the said prostaglandin EP4 receptor ligand is a 5,6,7-trinor-4,8-inter-m-phenylene PGI_2 derivative of the following Formula (I) or a pharmacologically acceptable salt thereof:

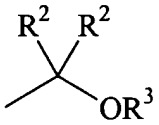


(I)

wherein

R^1 is

(i)



wherein R^2 is hydrogen, C_1-C_4 linear alkyl, C_3 or C_4 branched alkyl, trifluoromethyl, -C(=O)-R^4, or -C(=O)-O-R^4, wherein R^4 is C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl or substituted phenyl (wherein the substituent is at least one fluorine, chlorine, bromine, iodine, trifluoromethyl, C_1-C_4 alkyl, nitro, cyano, methoxy, phenyl, phenoxy, p-acetamidebenzamide, -CH=N-NH-C(=O)-NH_2, -NH-C(=O)-Ph, -NH-C(=O)-CH_3 or -NH-C(=O)-NH_2), and the two R^2s may be the same or different; R^3 is hydrogen, C_1-C_4 alkyl, C_1-C_{12} acyl, C_7-C_{16} aroyl, C_7-C_{16} aralkyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, allyl, tert-butyl or tert-butyldimethylsilyl,

(ii) -COOR^5

wherein R^5 is

(1) hydrogen or pharmacologically acceptable cation,

(2) C_1-C_{12} linear alkyl or C_3-C_{14} branched alkyl,

(3) -Z-R^6

wherein Z is a valence bond, or linear or branched alkylene represented by the formula C_tH_{2t} wherein t represents an integer of 1 to 6, R^6 is C_3-C_{12} cycloalkyl, or C_3-C_{12} cycloalkyl substituted with 1 to 4 R^7s wherein R^7 is hydrogen or C_1-C_5 alkyl,

(4) -$(CH_2CH_2O)_nCH_3$

wherein n represents an integer of 1 to 5,

(5) -Z-Ar

wherein Z is defined as the same as the above, Ar is phenyl, α-naphthyl, β-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, α-furyl, β-furyl, α-thienyl, β-thienyl or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above),

(6) -$C_tH_{2t}COOR^8$

wherein t is defined as the same as the above, R^8 is hydrogen or C_1-C_5 alkyl,

(7) -$C_tH_{2t}N(R^9)_2$

wherein t is defined as the same as above, R^9 is hydrogen or C_1-C_5 alkyl, and the two R^9s may be the same or different,

(8) -$CH(R^{10})$-C(=O)-R^{11}

wherein R^{10} is hydrogen or benzoyl, R^{11} is phenyl, p-bromophenyl, p-chlorophenyl, p-biphenyl, p-nitrophenyl, p-benzamidephenyl or 2-naphthyl,

(9) -C_pH_{2p}-W-R^{12}

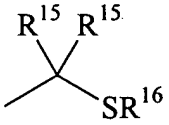
wherein p represents an integer of 1 to 5, W is -CH=CH-, -CH=C(R^{13})- or

-C≡C- wherein R^{13} is C_1-C_{30} linear alkyl, C_3-C_{30} branched alkyl or C_7-C_{30} aralkyl, R^{12} is hydrogen, C_1-C_{30} linear alkyl, C_3-C_{30} branched alkyl or C_7-C_{30} aralkyl, or

(10) $-CH(CH_2OR^{14})_2$

wherein R^{14} is C_1-C_{30} alkyl or C_1-C_{30} acyl, and the two R^{14}s may be the same or different,

(iii)



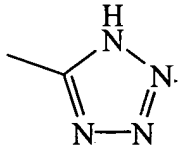
wherein R^{15} represents is hydrogen, C_1-C_4 linear alkyl, C_3 or C_4 branched alkyl, trifluoromethyl, $-C(=O)-R^{17}$ or $-C(=O)-O-R^{17}$ wherein R^{17} is C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), and the two R^{15}s may be the same or different; R^{16} is hydrogen, C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, phenyl or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), or

$-C(=O)-R^{18}$ wherein R^{18} represents C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above),

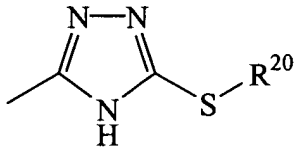
(iv) $-CH_2-R^{19}$

wherein R^{19} is

(1)

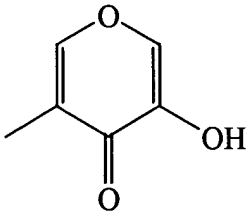


(2)

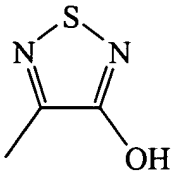


wherein R^{20} represents hydrogen, C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, phenyl, substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), or -C(=O)-R^{21} wherein R^{21} is C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl, or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above),

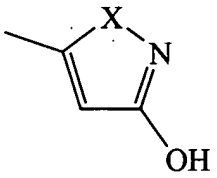
(3)



(4)



(5)



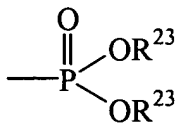
wherein X represents -O- or -S-, or

(6) azide,

(v) $-C(R^{22})_3$

wherein R^{22} represents hydrogen, fluorine, chlorine, bromine, iodine, cyano or C_1-C_4 alkyl, and all of the R^{22}s may be the same or different,

(vi)



wherein R^{23} represents hydrogen, C_1-C_4 alkyl, phenyl, substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), -CH_2-OR^{24} (wherein R^{24} is C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl, or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), or pharmacologically acceptable cation, and the two R^{23}s may be the same or different,

(vii) -$N(R^{25})_2$

wherein R^{25} is hydrogen, C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_4-C_{13} cycloalkylalkyl, C_7-C_{12} aralkyl, -C(=O)-R^{26},-C(=O)-O-R^{26}, -SO_2-R^{26}, phenyl or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), R^{26} is C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), the two R^{25}s may be the same or different (when one of the R^{25}s is -SO_2-R^{26}, the other R^{25} is not -SO_2-R^{26}),

(viii) -$(C(=O)CH_2)_k$-H

wherein k is an integer of 1 or 2, or

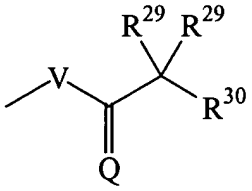
(ix) $-C(=O)-N(R^{27})_2$

wherein R^{27} is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, phenyl, substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), C_4-C_{13} cycloalkylalkyl, C_7-C_{12} aralkyl, cyano or $-SO_2-R^{28}$ wherein R^{28} is C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, phenyl, substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), C_4-C_{13} cycloalkylalkyl, or C_7-C_{12} aralkyl, and the two R^{27}s may be the same or different (when one of the R^{27}s is $-SO_2-R^{28}$, the other R^{27} is not $-SO_2-R^{28}$);

Y is hydrogen, C_1-C_4 alkyl, fluorine, chlorine, bromine, formyl, methoxy or nitro;

B is

(i)



wherein V is

(1) $-CH_2CH_2-$,

(2) $-C\equiv C-$,

or

(3) $-CH=C(R^{31})-$

wherein R^{31} is hydrogen, C_1-C_5 alkyl, fluorine, chlorine, bromine or iodine,

Q is

(1) =O

(2)

$$\begin{matrix} -R^{32} \\ -OR^{33} \end{matrix}$$

or

(3)

$$\begin{matrix} -R^{32} \\ -R^{32} \end{matrix}$$

wherein R^{32} is hydrogen, C_1-C_4 linear alkyl, C_3 or C_4 branched alkyl, trifluoromethyl, -C(=O)-R^{34}, or -C(=O)-O-R^{34} wherein R^{34} represents C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_7-C_{12} aralkyl, phenyl or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above); R^{33} is hydrogen, C_1-C_4 alkyl, C_1-C_{12} acyl, C_7-C_{16} aroyl, C_7-C_{16} aralkyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, allyl, tert-butyl or tert-butyldimethylsilyl, and the two R^{32}s may be the same or different; R^{29} is hydrogen, fluorine, chlorine, bromine, iodine, cyano or C_1-C_4 alkyl, and the two R^{29}s may be the same or different;

R^{30} is

(1) $-Z-R^{35}$

wherein Z is defined as the same as the above, R^{35} is C_1-C_{12} linear alkyl, C_3-C_{14} branched alkyl, C_3-C_{12} cycloalkyl, C_4-C_{13} cycloalkylalkyl, C_3-C_{12} cycloalkyl substituted with 1 to 4 R^{36}s (wherein R^{36} is hydrogen or C_1-C_5 alkyl), C_4-C_{13} cycloalkylalkyl substituted with 1 to 3 R^{36}s (wherein R^{36} is defined as the same as the above), phenyl, substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl mentioned above), α-naphthyl, β-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, α-furyl, β-furyl, α-thienyl or β-thienyl,

(2) $-Z-O-R^{35}$

wherein Z and R^{35} are defined as the same as the above,

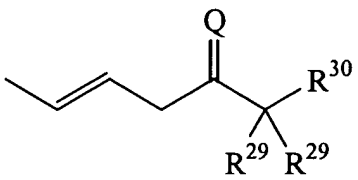
(3) $-Z-CH=C(R^{35})_2$

wherein Z and R^{35} are defined as the same as the above, and the two R^{35}s may be the same or different, or

(4) $-Z-C\equiv C-R^{35}$

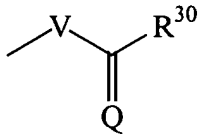
wherein Z and R^{35} are defined as the same as the above,

(ii)



wherein Q, R^{29} and R^{30} are defined as the same as the above, and the two R^{29}s may be the same or different, or

(iii)

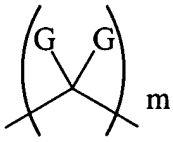


wherein V, Q and R^{30} are defined as the same as the above;

E represents hydrogen or $-OR^{33}$ wherein R^{33} is defined as the same as the above;

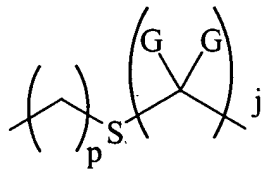
A is

(i)



wherein m represents an integer of 0 to 5, G represents hydrogen, fluorine, chlorine, bromine, iodine, trifluoromethyl, C_1-C_4 linear alkyl or C_3-C_6 branched alkyl, and all Gs may be the same or different,

(ii)



wherein j represents an integer of 1 to 4, p represents an integer of 0 or 1, G is defined as the same as the above, and all Gs may be the same or different,

(iii) $-CH=CH-CH_2-$,

(iv) $-CH_2-CH=CH-$,

(v) $-CH_2-O-CH_2-$,

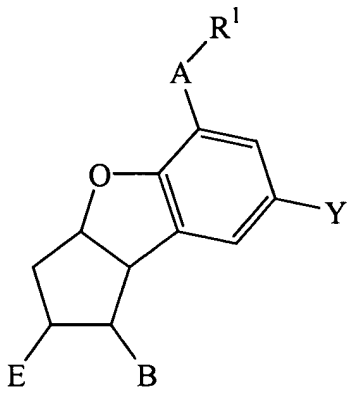
(vi) $-O-CH_2-$,

(vii) $-C\equiv C-$, or

(viii) -C=C- (trans).

---

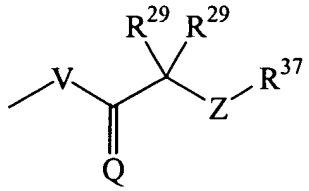
19. (Amended) The method according to claim 17, wherein the said 5,6,7-trinor-4,8-inter-m-phenylene PGI_2 derivative is represented by the following Formula (I) or a pharmacologically acceptable salt thereof:



(I)

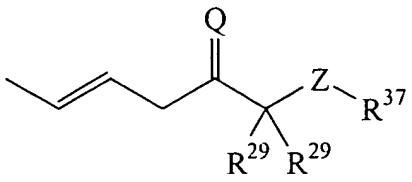
wherein R^1, Y, E and A are defined in claim 17, B is

(i)



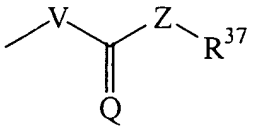
wherein V, Q, R^{29} and Z are defined in claim 17, the two R^{29}s may be the same or different, R^{37} is C_3-C_{12} cycloalkyl, C_4-C_{13} cycloalkylalkyl, C_3-C_{12} cycloalkyl substituted with 1 to 4 R^{38}s (wherein R^{38} is hydrogen or C_1-C_5 alkyl), C_4-C_{13} cycloalkylalkyl substituted with 1 to 3 R^{38}s (wherein R^{38} is defined as the same as the above), phenyl, substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl in claim 17), α-naphthyl, β-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, α-furyl, β-furyl, α-thienyl or β-thienyl,

(ii)



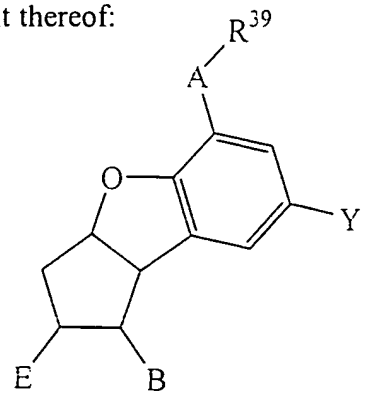
wherein Q, R^{29}, Z and R^{37} are defined as the same as the above, and the two R^{29}s may be the same or different, or

(iii)



wherein V, Q, Z and R^{37} are defined as the same as the above.

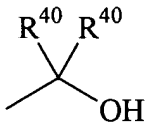
20. (Amended) The method according to claim 17, wherein the said 5,6,7-trinor-4,8-inter-m-phenylene PGI_2 derivative is represented by the following Formula (II) or a pharmacologically acceptable salt thereof:



(II)

wherein R^{39} is

(i)

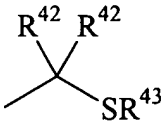


wherein R^{40} is hydrogen, C_1-C_4 linear alkyl or trifluoromethyl, the two R^{40} may be the same or different,

(ii) $-COOR^{41}$

wherein R^{41} is hydrogen, a pharmacologically acceptable cation or C_1-C_{12} linear alkyl,

(iii)

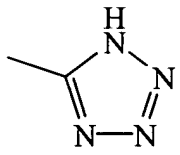


wherein R^{42} is hydrogen, C_1-C_4 linear alkyl or trifluoromethyl, the two R^{42}s may be the same or different, R^{43} is hydrogen, C_1-C_4 linear alkyl, phenyl, or $-C(=O)-R^{44}$ wherein R^{44} represents C_1-C_4 linear alkyl,

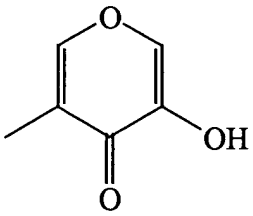
(iv) $-CH_2-R^{45}$

wherein R^{45} is

(1)



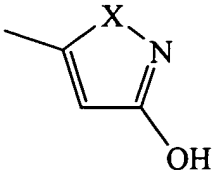
(2)



B3 cont.

or

(3)

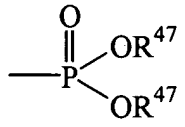


wherein X is defined in claim 17,

(v) $-C(R^{46})_3$

wherein R^{46} represents hydrogen, fluorine, cyano or C_1-C_4 alkyl, and all R^{46}s may be the same or different,

(vi)



wherein R^{47} represents hydrogen, C_1-C_4 alkyl, or a pharmacologically acceptable cation, and the two R^{47}s may be the same or different, or

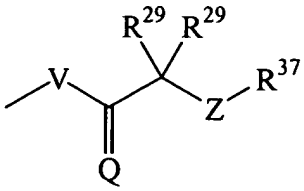
(vii) $-N(R^{48})_2$

wherein R^{48} is hydrogen, $-C(=O)-R^{49}$ or $-SO_2-R^{49}$ wherein R^{49} is C_1-C_4 linear alkyl or phenyl, and the two R^{48}s may be the same or different (when one of R^{48}s is $-SO_2-R^{49}$, the other R^{48} is not $-SO_2-R^{49}$),

Y is hydrogen, fluorine, chlorine or bromine,

B is

(i)



wherein V is

(1) $-CH_2CH_2-$,

(2) $-C\equiv C-$,

or

(3) -CH=CH-,

Q is

(1) =O,

(2)

$$\begin{array}{l} \text{—}R^{50} \\ \text{—}OR^{33} \end{array}$$

or

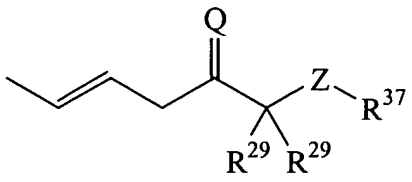
(3)

$$\begin{array}{l} \text{—}R^{50} \\ \text{—}R^{50} \end{array}$$

wherein R^{50} is hydrogen, C_1-C_4 linear alkyl, C_3 or C_4 branched alkyl, or trifluoromethyl, R^{33} is defined in claim 17, the two R^{50}s may be the same or different, R^{29} is defined in claim 17, and the two R^{29}s may be the same or different, Z is defined in claim 17, and R^{37} is C_3-C_{12} cycloalkyl, C_4-C_{13} cycloalkylalkyl, C_3-C_{12} cycloalkyl substituted with 1 to 4 R^{38}s (wherein R^{38}

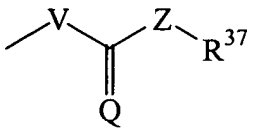
is hydrogen or C_1-C_5 alkyl), C_4-C_{13} cycloalkylalkyl substituted with 1 to 3 R^{38}s (wherein R^{38} is defined as the same as the above), phenyl, substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl in claim 17), α-naphthyl, β-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, α-furyl, β-furyl, α-thienyl or β-thienyl,

(ii)



wherein Q, R^{29}, Z and R^{37} are defined as the same as the above, and the two R^{29}s may be the same or different, or

(iii)

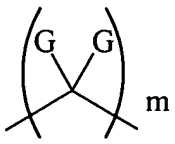


wherein V, Q, Z and R^{37} are defined as the same as the above,

E represents the following in the definition of claim 17,

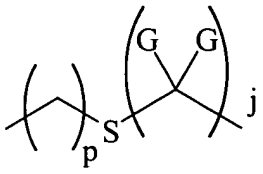
A is

(i)



wherein m represents an integer of 0 to 3, G is hydrogen, fluorine, chlorine, bromine, iodine, trifluoromethyl or C_1-C_4 linear alkyl, and all Gs may be the same or different,

(ii)



wherein j represents an integer of 1 or 2, p represents the following in the definition of claim 17, G is defined as the same as the above, and all Gs may be the same or different,

(iii) $-CH=CH-CH_2-$,

(iv) $-CH_2-CH=CH-$,

(v) $-CH_2-O-CH_2-$,

(vi) $-O-CH_2-$,

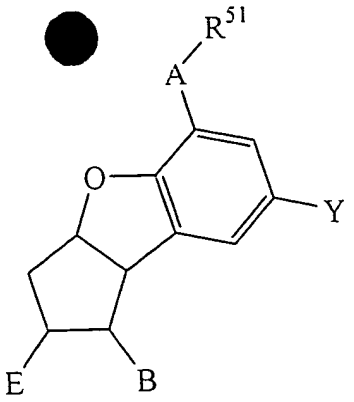
(vii) $-C\equiv C-$

or

(viii) -C=C- (trans).

B3 cont.

21. (Amended) The method according to claim 17, wherein the said 5,6,7-trinor-4,8-inter-m-phenylene PGI_2 derivative is represented by the following Formula (III) or a pharmacologically acceptable salt thereof:



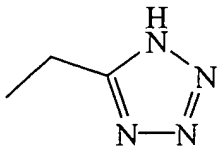
(III)

wherein R^{51} is

(i) $-COOR^{52}$

wherein R^{52} is hydrogen, a pharmacologically acceptable cation or methyl, or

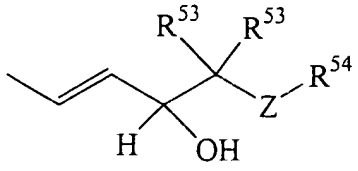
(ii)



wherein Y is hydrogen or fluorine,

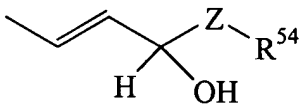
B is

(i)



wherein R^{53} is hydrogen, fluorine or C_1-C_4 alkyl, the two R^{53}s may be the same or different, Z represents the following in the definition of claim 17, R^{54} is C_5-C_7 cycloalkyl, phenyl, or substituted phenyl (wherein the substituent is the same as the substituent defined for the substituted phenyl in claim 17), or

(ii)

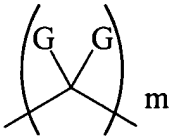


B3 cont.

wherein Z and R^{54} are defined as the same as the above,

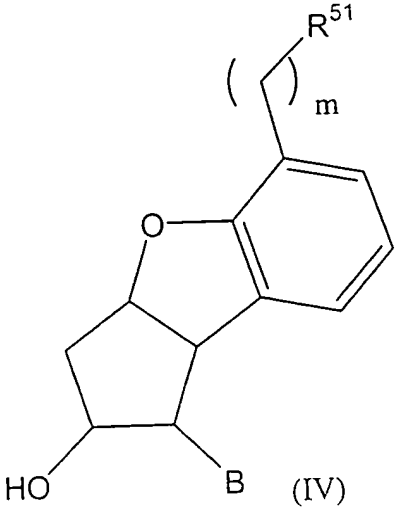
E is hydrogen or -OH,

A is



wherein m represents an integer of 0 to 2, G represents hydrogen or fluorine, and all Gs may be the same or different.

22. (Amended) The method according to claim 17, wherein the said 5,6,7-trinor-4,8-inter-m-phenylene PGI_2 derivative is represented by the following Formula (IV) or a pharmacologically acceptable salt thereof:



(IV)

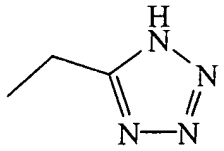
wherein R^{51} is

B3 cont.

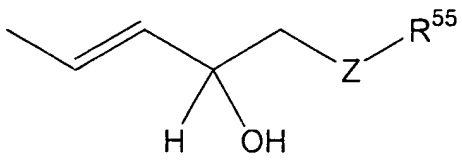
(i) $-COOR^{52}$

wherein R^{52} is hydrogen, a pharmacologically acceptable cation or methyl, or

(ii)

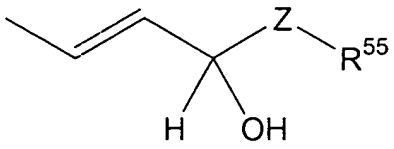


B is



(i)

wherein Z represents the following in the definition of claim 17, R^{55} is C_5-C_7 cycloalkyl or phenyl, or

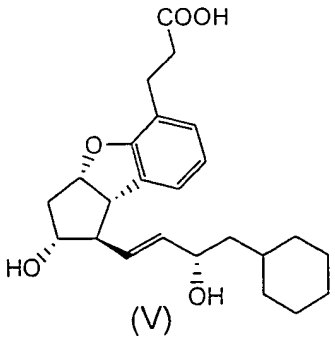


B3 CONT.

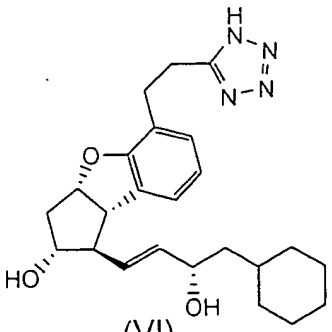
(ii)

wherein Z and R^{55} are defined as the same as the above, m represents an integer of 0 to 2.

23. (Amended) The method according to claim [22] 17, wherein the said 5,6,7-trinor-4,8-inter-m-phenylene PGI_2 derivative is represented by the [said] following Formula (V) or (VI):



(V)



(VI)

24. (Amended) The method according to any one of claims 17 and 19 to 23, wherein the said method for modulating growth or generation of hair is a method for promoting growth or generation of hair.

B4